



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 600

[Docket No. FDA-2017-N-7007]

RIN 0910-AH49

Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products; Companion to Direct Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is proposing to amend the general biologics regulations relating to time of inspection requirements and also removing duties of inspector requirements. FDA is proposing this action to remove outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug establishments, thereby providing flexibility without diminishing public health protections. This action is part of FDA's implementation of Executive Orders (EOs) 13771 and 13777. Under these EOs, FDA is comprehensively reviewing existing regulations to identify opportunities for repeal, replacement, or modification that will result in meaningful burden reduction while allowing the Agency to achieve our public health mission and fulfill statutory obligations.

DATES: Submit either electronic or written comments on the proposed rule or its companion direct final rule by [INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. If FDA receives any timely significant adverse comments on the direct final rule with which this proposed rule is associated, the Agency will publish a document

withdrawing the direct final rule within 30 days after the comment period ends. FDA will apply any significant adverse comments received on the direct final rule to the proposed rule in developing the final rule. FDA will then proceed to respond to comments under this proposed rule using the usual notice and comment procedures.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until midnight Eastern Time at the end of [INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in

the body of your comments, that information will be posted on
<https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions.”)

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2017-N-7007 for “Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT

CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Melissa Segal, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to amend the general biologics regulations relating to time of inspection requirements and to remove duties of inspector requirements. FDA is proposing this action to remove outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug establishments, thereby providing flexibility without diminishing public health protections.

B. Summary of the Major Provisions of the Proposed Rule

This proposed rule would revise the time of inspection requirements contained in § 600.21 (21 CFR 600.21) and also remove the duties of inspector requirements contained in § 600.22 (21 CFR 600.22). These changes to the biological product regulations would eliminate outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug establishments, thereby providing flexibility without diminishing public health protections. Revision and removal of these regulations would not change the biological product establishment inspection requirements and duties of an investigator requirements that apply under sections 704 and 510(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 374 and 360(h)) and section 351(c) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(c)).

C. Legal Authority

FDA is proposing this action under the biological product provisions of the PHS Act, and the drugs and general administrative provisions of the FD&C Act, including sections 704 and 510(h) of the FD&C Act and section 351(c) of the PHS Act.

D. Costs and Benefits

Because this proposed rule would not impose any additional regulatory burdens, this regulation is not anticipated to result in any compliance costs and the economic impact is expected to be minimal.

II. Companion Document to Direct Final Rulemaking

This proposed rule is a companion to the direct final rule published in the rules section of this issue of the *Federal Register*. This companion proposed rule provides the procedural framework to finalize the rule in the event that the direct final rule receives any significant adverse comment and is withdrawn. The comment period for this companion proposed rule runs concurrently with the comment period for the direct final rule. Any comments received in response to this companion proposed rule will also be considered as comments regarding the direct final rule. FDA is publishing the direct final rule because we believe the rule contains noncontroversial changes and there is little likelihood that there will be significant adverse comments opposing the rule.

A significant adverse comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. In determining whether an adverse comment is significant and warrants terminating a direct final rulemaking, we will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process. Comments that are frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. A comment recommending a regulation change in addition to those in the direct final rule would not be considered a significant adverse comment unless the comment states why the rule would be ineffective without the additional change. In addition, if a significant adverse comment applies to a part of

the direct final rule and that part can be severed from the remainder of the rule, we may adopt as final those provisions of the rule that are not the subject of the significant adverse comment.

If any significant adverse comments to the direct final rule are received during the comment period, FDA will publish, within 30 days after the comment period ends, a notice of significant adverse comment and withdraw the direct final rule. If we withdraw the direct final rule, any comments received will be considered comments on the proposed rule and will be considered in developing a final rule using the usual notice-and-comment procedure.

If no significant adverse comment is received in response to the direct final rule during the comment period, no further action will be taken related to this proposed rule. Instead, we will publish a document confirming the effective date within 30 days after the comment period ends. Additional information about direct final rulemaking procedures is set forth in the document entitled “Guidance for FDA and Industry: Direct Final Rule Procedures,” announced and provided in the *Federal Register* of November 21, 1997 (62 FR 62466). The guidance may be accessed at: <https://www.fda.gov/RegulatoryInformation/Guidances/ucm125166.htm>.

III. Background

On February 24, 2017, President Donald Trump issued Executive Order 13777, “Enforcing the Regulatory Reform Agenda” (82 FR 12285, March 1, 2017). One of the provisions in the Executive Order requires Agencies to evaluate existing regulations and make recommendations to the Agency head regarding their repeal, replacement, or modification, consistent with applicable law. As one step in implementing the Executive Order, FDA published a notice in the *Federal Register* of September 8, 2017 (82 FR 42492) entitled “Review of Existing Center for Biologics Evaluation and Research Regulatory and Information Collection Requirements.” In that notice, FDA announced that it was conducting a review of existing

regulations to determine, in part, whether they can be made more effective in light of current public health needs and to take advantage of, and support, advances in innovation that have occurred since those regulations took effect. As part of this initiative, FDA is updating outdated regulations as specified in this rule.

FDA's general biological products regulations in part 600 (21 CFR part 600) are intended to help ensure the safety, purity, and potency of biological products administered to humans. The proposed revision and removal of certain general biological products regulations are designed to eliminate outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug establishments and provide flexibility without diminishing public health protections.

A. Section 600.21

The authority for FDA to conduct establishment inspections is included in both the FD&C Act and the PHS Act. Specifically, section 704 of the FD&C Act and section 351(c) of the PHS Act authorize the Agency to inspect establishments that manufacture biological products. Before July 9, 2012--the date the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144) was signed into law--section 510(h) of the FD&C Act further provided, among other things, that drug and device establishments registered with FDA must be inspected at least once in the 2-year period beginning with the date of registration and at least once in every successive 2-year period thereafter. Section 510(h) of the FD&C Act applies to biological product establishments because all biological products are subject to regulation under the drug or device provisions of the FD&C Act (in addition to the biological product provisions of the PHS Act). Since 1983, FDA's biological product regulation at § 600.21 has also included a biennial inspection requirement ("[A]n inspection of each licensed

establishment and its additional location(s) shall be made at least once every 2 years”); this was consistent with the pre-FDASIA biennial inspection requirement in section 510(h) of the FD&C Act.

With the enactment of FDASIA, however, the biennial inspection requirement for drug establishments in section 510(h) of the FD&C Act was replaced with a requirement that FDA inspect drug establishments in accordance with a risk-based schedule established by FDA. Accordingly, for biological product establishments that are registered as drug establishments under section 510(h), the requirement in § 600.21 regarding the frequency of inspections is no longer consistent with the FD&C Act and is outdated (e.g., the risk-based inspection schedule for drug establishments may result in scheduling inspections at intervals of greater than 2 years for certain biological product establishments). For this reason, and to provide for greater flexibility in general with respect to determining the frequency of biological product establishment inspections under the authority provided in the FD&C Act and the PHS Act, FDA proposes to revise § 600.21 to remove the biennial inspection requirement for biological product establishments that are registered as drug establishments and for those that are registered as device establishments.

In addition, § 600.21 includes provisions concerning inspectional notice and the timing of pre-licensure reinspections of biological product establishments. These provisions are outdated and unnecessary. Inspectional notice is addressed in the Agency’s practices for inspections in its Standard Operating Procedures and Policies and in the Investigations Operations Manual (IOM). With respect to the timing of a reinspection of a biological product establishment following the denial of a biologics license application, the general biologics licensing provision at 21 CFR 601.4, which was issued subsequent to § 600.21, sets forth the administrative procedures

following the denial of a license; accordingly, the specific provision in § 600.21 regarding timing of a reinspection following denial of a license is unnecessary. Therefore, FDA is proposing to remove these provisions.

B. Section 600.22

Current § 600.22 requires specific duties of an FDA inspector. These existing codified requirements are unnecessary because they are duplicative of statutory requirements that apply to biological product inspections under section 704 of the FD&C Act. Specifically, the inspection requirements in section 704 of the FD&C Act encompass all of the requirements outlined in § 600.22. Thus, we are proposing to remove § 600.22(a) through (h).

The removal of these regulations, however, would not change the establishment inspection requirements and duties of an investigator requirements specified in sections 704 and 510(h) of the FD&C Act, section 351(c) of the PHS Act, or the procedures described in the IOM. Additionally, it would not change the established process for risk-based inspection planning and work planning.

IV. Highlights of the Proposed Rule

FDA is proposing to amend the general biologics regulations by revising time of inspection requirements contained in § 600.21 and also by removing the duties of inspector requirements contained in § 600.22. These proposed changes are designed to remove the existing codified requirements that are outdated and to accommodate new approaches, such as a risk-based inspection frequency for biological product establishments, thereby providing flexibility without diminishing public health protections.

V. Legal Authority

FDA is issuing this proposed rule under the biological products provisions of the PHS Act (42 U.S.C. 216, 262, 263, 263a, 264, and 300aa-25) and the drugs and general administrative provisions of the FD&C Act (21 U.S.C. 321, 351, 352, 353, 355, 356c, 356e, 360, 360i, 371, 374, and 379k-l). Under these provisions of the PHS Act and the FD&C Act, we have the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, and potent, and prevent the introduction, transmission, and spread of communicable disease.

VI. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations “shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.” We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule does not impose any additional regulatory burdens, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$148 million, using the most current (2016) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

This proposed rule proposes amendments to the general biologics regulations by removing time of inspection requirements and the duties of inspector requirements. FDA is proposing this action to remove outdated requirements, accommodate new approaches, and provide flexibility without diminishing public health protections. Because this rulemaking proposes removal of regulations to be consistent with updated practice and does not impose any additional regulatory burdens, this proposed rulemaking is not anticipated to result in any compliance costs and the economic impact is expected to be minimal.

VII. Analysis of Environmental Impact

We have determined under 21 CFR 25.31(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National

Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Paperwork Reduction Act of 1995.

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

List of Subjects in 21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 600 be amended as follows:

PART 600--BIOLOGICAL PRODUCTS: GENERAL

1. The authority citation for part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 356c, 356e, 360, 360i, 371, 374, 379k-l; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25.

§ 600.21 [Amended]

2. Amend § 600.21 by removing the last three sentences.

§ 600.22 [Removed and Reserved]

3. Remove and reserve § 600.22.

Dated: January 23, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-01467 Filed: 1/25/2018 8:45 am; Publication Date: 1/26/2018]